#2

PATENTS • DESIGNS • COPYRIGHT • TRADE MARKS
The Patent Office

INVESTOR IN PEOPLE

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

-registration under the Companies Act does not constitute a new legal entity but merely jects the company to certain additional company law rules.

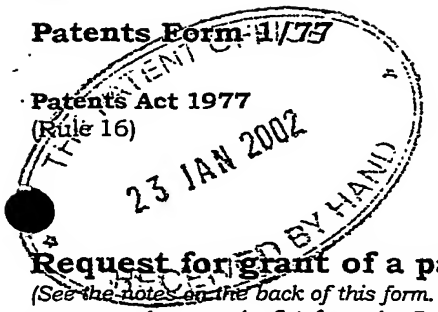
CERTIFIED COPY OF PRIORITY DOCUMENT

Signed

Dated 31 JAN 2003

Patents Form 1/77

Patents Act 1977
(Rule 16)



The **Patent Office**

1/77

24JAN02 E659214-1 000572
P01/7700 0.00-0201508.9

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office
Cardiff Road
Newport
Gwent NP10 8QQ

1.	Your reference	4-32325P1	
2.	Patent application number *(The Patent Office will fill in this part)*	23 JAN 2002	0201508.9
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	NOVARTIS AG LICHTSTRASSE 35 4056 BASEL SWITZERLAND	
	Patent ADP number *(if you know it)*	GB2548740005	
	If the applicant is a corporate body, give the country/state of its incorporation	SWITZERLAND	
4.	Title of invention	Organic Compounds	
5.	Name of your agent *(If you have one)*		
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	B.A. YORKE & CO. CHARTERED PATENT AGENTS COOMB HOUSE, 7 ST. JOHN'S ROAD ISLEWORTH MIDDLESEX TW7 6NH	
	Patents ADP number *(if you know it)*	1800001 ✓	

6.	If you are declaring priority from one ore more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of filing (day/month/year)

7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing (day/month/year)

8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:* *a) any applicant named in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body.* *(see note (d))*	Yes

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	27
Claim(s)	4
Abstract	
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	ONE
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application

Signature B.A. Yorke & Co. Date B.A. Yorke & Co. 23 January 2002

12. Name and daytime telephone number of person to contact in the United Kingdom

Mrs. E. Cheetham
020 8560 5847

Warning

After an application for a patent has been filed. the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the united Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.

b) Write your answers in capital letters using black ink or you may type them.

c) If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.

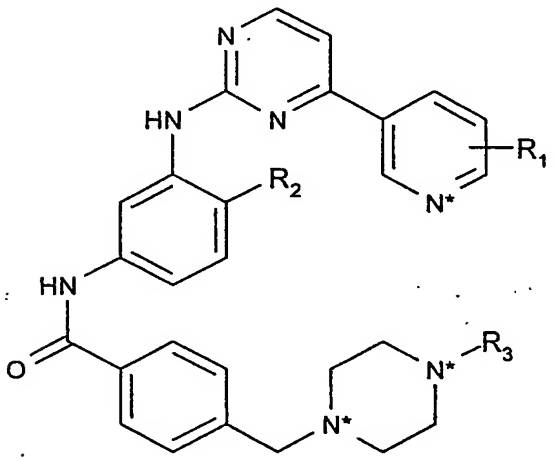
d) Once you have filled in the form you must remember to sign and date it.

e) For details of the fee and ways to pay please contact the Patent Office.

Organic Compounds

The invention relates to *N*-{3-[4-(piperazino-methyl)-benzoylamido]-phenyl}-4-(3-pyridinyl)-2-pyrimidine-amine derivatives, to processes for the preparation thereof, to pharmaceutical compositions comprising those compounds, and to the use thereof in the preparation of pharmaceutical compositions for the therapeutic treatment of warm-blooded animals, including humans.

The invention relates to compounds of formula I



(I),

wherein

R_1 is hydrogen or hydroxy,

R_2 is lower alkyl or hydroxy-lower alkyl,

R_3 is hydrogen, methyl or acetyl, and

the stars indicate the nitrogen atoms which optionally carry an oxygen atom to form the corresponding N-oxides,

with the proviso that at least one of the three nitrogen atoms marked by a star carries an oxygen atom if R_1 is hydrogen, R_2 is methyl and R_3 is hydrogen or methyl,

or salts of such compounds.

The term "lower" within the scope of this text denotes radicals having up to and including 7, preferably up to and including 4 carbon atoms.

When R_1 is hydroxy, the 3-pyridinyl moiety is substituted by hydroxy at a ring carbon atom at position 2, 4, 5 or 6.

Lower alkyl R_2 is preferably methyl.

Hydroxy-lower alkyl R_2 is preferably hydroxymethyl.

Salts are especially the pharmaceutically acceptable salts of compounds of formula I.

Such salts are formed, for example, as acid addition salts, preferably with organic or inorganic acids, from compounds of formula I with a basic nitrogen atom, especially the pharmaceutically acceptable salts.

For isolation or purification purposes it is also possible to use pharmaceutically unacceptable salts, for example picrates or perchlorates. Only the pharmaceutically acceptable salts or free compounds (if the occasion arises, in the form of pharmaceutical compositions) attain therapeutic use, and these are therefore preferred.

In view of the close relationship between the novel compounds in free form and in the form of their salts, including those salts that can be used as intermediates, for example in the purification or identification of the novel compounds, hereinbefore and hereinafter any reference to the free compounds is to be understood as referring also to the corresponding salts, as appropriate and expedient.

A compound of formula I possesses valuable pharmacological properties and may, for example, be used as an anti-tumour agent, as an agent to treat atherosclerosis, as an agent to treat restenosis, for the prevention of transplantation-induced disorders, such as obliterative bronchiolitis, and/or for preventing the invasion of warm-blooded animal cells by certain bacteria, such as *Porphyromonas gingivalis*.

The phosphorylation of proteins has long been known as an essential step in the differentiation and division of cells. Phosphorylation is catalysed by protein kinases subdivided into serine/threonine and tyrosine kinases. The tyrosine kinases include PDGF (Platelet-derived Growth Factor) receptor tyrosine kinase.

PDGF is a very commonly occurring growth factor, which plays an important role both in normal growth and also in pathological cell proliferation, such as is seen in carcinogenesis and in diseases of the smooth-muscle cells of blood vessels, for example in atherosclerosis and thrombosis.

The inhibition of PDGF-stimulated receptor tyrosine kinase activity *in vitro* is measured in PDGF receptor immune complexes of A431 cells, as described by E. Andrejauskas-Buchdunger and U. Regenass in Cancer Research 52, 5353-5358 (1992). A compound of formula I inhibits PDGF-dependent acellular receptor phosphorylation. The inhibition of PDGF receptor tyrosine kinase is measured in a microtitre ELISA assay (*cf* Trinks et al., J. Med. Chem. 37, 1015-27 (1994).

The inhibition of PDGF receptor tyrosine kinase makes a compound of formula I also suitable for the treatment of tumour diseases, such as gliomas, sarcomas, prostate tumours, and tumours of the colon, breast, and ovary.

A compound of formula I also inhibits cellular processes involving the so-called stem-cell factor (SCF, also known as the c-Kit ligand or steel factor), such as SCF receptor (Kit) autophosphorylation and the SCF-stimulated activation of MAPK kinase (mitogen-activated protein kinase).

In particular, a compound of formula I inhibits the tyrosine kinase activity of c-Kit. This can be shown in a tyrosine kinase inhibition assay using the cytoplasmatic kinase domain of c-Kit. The assay is performed as follows: The baculovirus donor vector pFbacG01 (GIBCO) is used to generate a recombinant baculovirus that expresses the amino acid region amino acids 544-976 of the cytoplasmic kinase domains of human c-Kit. The coding sequences for the cytoplasmic domain of c-Kit is amplified by PCR from a human uterus c-DNA library (Clontech). The amplified DNA fragment and the pFbacG01 vector are made compatible for ligation by digestion with BamH1 and EcoRI. Ligation of these DNA fragments results in the baculovirus donor plasmid c-Kit. The production of the viruses, the expression of proteins in Sf9 cells and the purification of the GST-fused proteins are performed as follows: *Production of virus*: Transfer vector (pFbacG01-c-Kit) containing the c-Kit kinase domain is transfected into the DH10Bac cell line (GIBCO) and the transfected cells are plated on

selective agar plates. Colonies without insertion of the fusion sequence into the viral genome (carried by the bacteria) are blue. Single white colonies are picked and viral DNA (bacmid) is isolated from the bacteria by standard plasmid purification procedures. Sf9 cells or Sf21 cells (American Type Culture Collection) are then transfected in 25 cm^2 flasks with the viral DNA using Cellfectin reagent.

Determination of small scale protein expression in Sf9 cells: Virus containing media is collected from the transfected cell culture and used for infection to increase its titre. Virus containing media obtained after two rounds of infection is used for large-scale protein expression. For large-scale protein expression 100 cm^2 round tissue culture plates are seeded with 5 x 10^7 cells/plate and infected with 1 mL of virus-containing media (approx. 5 MOIs). After 3 days the cells are scraped off the plate and centrifuged at 500 rpm for 5 min. Cell pellets from 10-20, 100 cm^2 plates, are resuspended in 50 mL of ice-cold lysis buffer (25 mM Tris-HCl, pH 7.5, 2 mM EDTA, 1% NP-40, 1 mM DTT, 1 mM PMSF). The cells are stirred on ice for 15 min and then centrifuged at 5000 rpms for 20 min.

Purification of GST-tagged protein: The centrifuged cell lysate is loaded onto a 2 mL glutathione-sepharose column (Pharmacia) and washed three times with 10 mL of 25 mM Tris-HCl, pH 7.5, 2 mM EDTA, 1 mM DTT, 200 mM NaCl. The GST-tagged protein is eluted by 10 applications (1 mL each) of 25 mM Tris-HCl, pH 7.5, 10 mM reduced-glutathione, 100 mM NaCl, 1 mM DTT, 10 % Glycerol and stored at -70°C.

Kinase assay: Tyrosine protein kinase assays with purified GST-c-Kit are carried out in a final volume of 30 µL containing 200-1800 ng of enzyme protein (depending on the specific activity), 20 mM Tris-HCl, pH 7.6, 3 mM $MnCl_2$, 3 mM $MgCl_2$, 1 mM DTT, 10 µM Na_3VO_4 , 5 µg/mL poly(Glu,Tyr) 4:1, 1 % DMSO, 1.0 µM ATP and 0.1 µCi [γ^{33} P] ATP. The activity is assayed in the presence or absence of inhibitors, by measuring the incorporation of ^{33}P from [$\gamma^{33}P$] ATP into the poly(Glu,Tyr) 4:1 substrate. The assay (30 µL) is carried out in 96-well plates at ambient temperature for 20 min under conditions described below and terminated by the addition of 20 µL of 125 mM EDTA. Subsequently, 40 µL of the reaction mixture is transferred onto Immobilon-PVDF membrane (Millipore, Bedford, MA, USA) previously soaked for 5 min with methanol, rinsed with water, then soaked for 5 min with 0.5 % H_3PO_4 and mounted on vacuum manifold with disconnected vacuum source. After spotting all samples, vacuum is connected and each well rinsed with 200 µL 0.5 % H_3PO_4. Membranes are removed and washed 4 x on a shaker with 1.0 % H_3PO_4 and once with ethanol. Membranes are counted after drying at ambient temperature, mounting in Packard TopCount 96-well frame, and addition of 10 µL/well of Microscint TM (Packard). IC_{50} values

are calculated by linear regression analysis of the percentage inhibition of each compound in duplicate, at four concentrations (usually 0.01, 0.1, 1 and 10 μM). One unit of protein kinase activity is defined as 1 nmole of ^{33}P ATP transferred from [$\gamma^{33}P$] ATP to the substrate protein per minute per mg of protein at 37 °C.

A compound of formula I inhibits also the autophosphorylation of SCF receptor (and c-Kit, a proto-oncogen). Inhibition of the autophosphorylation of the SCF receptor can be measured using e.g. MO7e cells, a human promegakaryocytic leukaemia cell line which depends on SCF for proliferation. They are obtained from Grover Bagby, Oregon Health Sciences University, USA. The cells are cultivated in RPMI 1649 medium supplemented with 10 FBS and 2.5 ng/ml GC-CMF. GM-SCF and SCF are commercially available. Serum-deprived MO7e cells are prepared and incubated for 90 min at 37 °C with the test substance before being stimulated with recombinant SCF for 10 min at 37 °C. Identical quantities of cell lysates are analysed by Western blot using antiphosphotyrosine antibodies (Buchdunger et al., Proc. Natl. Acad. Sci (USA) 92, 2558-62 (1995)). The immunodecorated proteins are detected by means of the ECL Western blotting system from Amersham (Amersham, UK).

On the basis of the described properties, a compound of formula I may be used not only as a tumour-inhibiting substance, for example in small cell lung cancer, but also as an agent to treat non-malignant proliferative disorders, such as atherosclerosis, thrombosis, psoriasis, scleroderma, and fibrosis, as well as for the protection of stem cells, for example to combat the haemotoxic effect of chemotherapeutic agents, such as 5-fluoruracil, and in asthma. It may especially be used for the treatment of diseases which respond to an inhibition of the PDGF receptor kinase.

In addition, a compound of formula I prevents the development of multidrug resistance in cancer therapy with other chemotherapeutic agents or abolishes a pre-existing resistance to other chemotherapeutic agents. Also regardless of the effect described hereinbefore, a compound of formula I may be used to advantage in combination with other antitumour agents, such as especially other c-Kit inhibitors and inhibitors of Vascular Endothelial Growth Factor (VEGF) receptor or c-Src activity.

Also Abl kinase, especially v-Abl kinase, is inhibited by a compound of formula I. The inhibition of v-Abl tyrosine kinase is determined by the methods of N. Lydon *et al.*, Oncogene

Research 5, 161-173 (1990) and J. F. Geissler *et al.*, Cancer Research 52, 4492-8 (1992). In those methods [Val^5]-angiotensin II and [γ $^{-32}$P]-ATP are used as substrates.

By analogy, a compound of formula I also inhibits Bcr-Abl kinase (see Nature Medicine 2, 561-566 (1996)) and is thus suitable for the treatment of Bcr-Abl-positive cancer and tumour diseases, such as leukaemias (especially chronic myeloid leukaemia and acute lymphoblastic leukaemia, where especially apoptotic mechanisms of action are found), and also shows effects on the subgroup of leukaemic stem cells as well as potential for the purification of these cells *in vitro* after removal of said cells (for example, bone marrow removal) and reimplantation of the cells once they have been cleared of cancer cells (for example, reimplantation of purified bone marrow cells).

In addition, a compound of formula I shows useful effects in the treatment of disorders arising as a result of transplantation, for example, allogenic transplantation, especially tissue rejection, such as especially obliterative bronchiolitis (OB), i.e. a chronic rejection of allogenic lung transplants. In contrast to patients without OB, those with OB often show an elevated PDGF concentration in bronchoalveolar lavage fluids. If a compound of formula I is administered to rats with tracheal allogenic transplants, for example in a dose of 50 mg/kg i.p., it can be shown after removal of 10 transplants per group after 10 and 30 days for morphometric analysis of possible epithelial lesions and occlusion of the airways, and investigation for immunohistochemical pathways of action that, although a compound of formula I has no significant effect on epithelial necrosis or infiltration by inflammatory cells, it does markedly reduce fibroproliferation and occlusion of the lumen compared with controls. Synergistic effects with other immunomodulatory or anti-inflammatory substances are possible, for example when used in combination with cyclosporin A (CsA), rapamycin, or ascomycin, or immunosuppressant analogues thereof, for example cyclosporin G, FK-506 or comparable compounds; corticosteroids; cyclophosphamide; azathioprine; methotrexate; brequinar; leflunomide; mizoribine; mycophenolic acid; mycophenolate mofetil; 15-deoxyspergualin; immunsuppressant antibodies, especially monoclonal antibodies for leucocyte receptors, for example MHC, CD2, CD3, CD4, CD7, CD25, CD28, B7, CD45, CD58 or their ligands; or other immunomodulatory compounds, such as CTLA4Ig. If CsA (1 mg/kg s.c.), for example, is combined with a compound of formula I (50 mg/kg), synergism may be observed.

A compound of formula I is also effective in diseases associated with vascular smooth-muscle cell migration and proliferation (where PDGF and PDGF receptor often also play a role), such as restenosis and atherosclerosis. These effects and the consequences thereof for the proliferation or migration of vascular smooth-muscle cells *in vitro* and *in vivo* can be demonstrated by administration of a compound of formula I and also by investigating its effect on the thickening of the vascular intima following mechanical injury *in vivo*.

A compound of formula I is used in 0.1N HCl or DMSO at a concentration of 10 mM for *in vitro* studies. The stock solution is further diluted with cell culture medium and used in concentrations of 10 to 0.1 μM for the experiments. For *in vivo* administration, a compound of formula I is dissolved for example in DMSO at a concentration of 200 mg/ml and then diluted 1:20 with 1% Tween in 0.9% saline solution. After sonication, a clear solution is obtained. The stock solutions are prepared fresh each day before administration. (The compound of formula I may also be dissolved simply in deionised water for oral administration or in 0.9% saline solution for parenteral administration). Administration is carried out 24 hours before the operation. A compound of formula I is administered to rats in one dose of 50 mg/kg i.p. per day for the entire observation period. Control rats are given the same formulation but without the presence of a compound of formula I. Oral administration is also possible.

Primary cultures of smooth-muscle aorta cells are isolated from 9 to 11-day-old DA (AG-B4, RT1a) rat aorta using a modification of the method described by Thyberg et al. (see Differentiation 25, 156-67 (1983)). The aorta is opened by means of a longitudinal incision and the endothelium carefully removed. The adventitia and the tunica media are separated, and the tunica media is digested with 0.1% collagenase and DNAse in phosphate-buffered physiological saline for 30 min at 37 °C. The cells are centrifuged, suspended in culture medium, and then allowed to grow on plastic vials. The primary cells are used for the experiments after passages 2 to 6. Subcultures are kept in DMEM (Dulbecco's Modified Eagle's Medium), supplemented with 10% fetal calf serum, 2 mmol/ml glutamine, 100 mmol/ml streptomycin, and 100 IU/ml penicillin. For identification purposes, the cells are left to grow on glass slide covers and stained immunohistochemically using an anti-α-actin antibody obtained from smooth-muscle cells (see below).

The migration of smooth-muscle cells is quantified *in vitro* using a Transwell cell culture insert (Costar, Cambridge, MA) whose upper and lower compartments are separated by a polycarbonate membrane of 8 μm pore size. The cells (100 μl at a concentration of 1 million cells/ml) are exposed in the upper compartment. After 2 hours, 60 ng/ml PDGF-BB or PDGF-AA (Upstate Biotechnology Inc., Lake Placid, NY) is added to the lower compartment, supplemented with 0.5% fetal calf serum and 0.1% bovine serum albumin, and the test compound of formula I is added in concentrations of 3, 1, 0.3, 0.1, 0.03, 0.01, and 0.003 μM. To measure fibronectin-dependent migration, the Transwell chambers are covered with fibronectin at a concentration of 10 μg/ml for 24 h at 4 °C (human cellular fibronectin, Upstate Biotechnology Inc.). After 24 hours' migration, the filters are removed, fixed in methanol, and stained with Mayer's haematoxylin and eosin. The migrated cells on the lower side of the filter membrane are determined by counting the specified sectional fields on the filters with the aid of a light microscope with a magnification of 400x. The inhibition of migration is quantified in terms of the percentage of cells versus with the control. To exclude the possibility of a toxic effect, the viability of the cells is tested by incorporation of 3H-thymidine in DMEM, supplemented with 10% fetal calf serum. An inhibition of migration induced by PDGF-AA and especially by PDGF-BB is observed with a compound of formula I.

Experimental animals: the aorta and carotid artery of male Wistar rats (purchased from the Laboratory Animal Centre of the University of Helsinki, Finland) are denuded. The rats are anaesthetised with 240 mg/kg chloral hydrate i.p. and Buprenorphine (Temgesic, Reckitt & Coleman, Hull, UK) is administered for perioperative and postoperative alleviation of pain. All animals are given human care in keeping with the "Principles of Laboratory Animal Care" and the "Guide for the Care and Use of Laboratory Animals" of the NIH (NIH Publication 86-23, revised 1985). Rats weighing 200-300 g were used for the denudation procedure. The left common carotid artery is denuded of endothelium through the intraluminal passage of a 2F embolectomy catheter (Baxter Healthcare Corporation, Santa Ana, CA, 27). To remove the endothelium, the catheter is passed through the lumen three times, inflated with 0.2 ml air. The external carotid is ligated after removal of the catheter and the wound closed. The histological changes are evaluated by reference to sections of mid-carotid 4 days after denudation. The thoracic aorta is denuded of endothelium using a 2F Fogarty arterial embolectomy catheter. The catheter is inserted into the thoracic aorta via the left iliac artery, inflated with 0.2 ml air, and passed through the lumen five times to remove the endothelium.

The iliac artery is then ligated. Three times (3, 7 and 14 days) are selected for evaluation of the histological changes.

To quantify the proliferating cells, 3 different procedures are used for labelling the cells with bromodeoxyuridine (BrdU) after denudation of the rat carotid. In this model, the media cell proliferation begins 24 h after denudation; cells in the intima first appear after 72-96 hours. To quantify the proliferation of smooth-muscle cells before the appearance of cells in the intima, 0.1 ml BrdU-labelling reagent (ZYMED, San Francisco, CA) is administered i.v. during the postoperative period of 0 to 72 h post-denudation (in total 0.1 ml 6 times). To quantify the proliferation during the initial wave of migration, the rats were given 3 x 0.1 ml BrdU-labelling reagent at 8-hour intervals over a period of 72-96 hours after the operation. To quantify the proliferation at the end of the initial wave of migration, a third group of rats is given a pulsed dose of 0.3 ml BrdU three hours before sacrifice.

Histological samples are fixed in 3% paraformaldehyde solution for 4 h for embedding in paraffin. Morphological changes are evaluated from paraffin sections stained with Mayer's haematoxylin-eosin. The cell counts of different vessel sections are calculated at a magnification of 400x. To identify cells in culture and cells appearing in the neo-intima within four days of the denudation injury, immunohistochemical staining of acetone-fixed samples is carried out using an anti-α-actin antibody obtained from smooth-muscle cells (Bio-Makor, Rehovot, Israel). Primary smooth-muscle cells are identified on acetone-fixed glass cover slides using the same staining method. The sections are incubated with the primary antibody (dilution 1:2000), washed, and incubated consecutively with peroxidase-conjugated rabbit-antimouse-Ig and goat-antirabbit-Ig, followed by treatment with substrate solution with the chromogen 3-amino-9-ethylcarbazol and hydrogen peroxide. BrdU stains are prepared from paraffin sections using a primary mouse antibody (Bu20a, Dako, A/S, Denmark) and the Vectastain Elite ABC-Kit (Vector Laboratories, Burliname, CA). The sections are deparaffinised and treated by microwave at 500 W (2 x 5 min in 0.1M citrate buffer, pH 6), followed by treatment with 95% formamide in 0.15 M trisodium citrate for 45 min at 70 °C. Antibody dilutions are prepared according to the manufacturer's specifications. The sections are counterstained with Mayer's haematoxylin and eosin, and positive cells are counted separately for the initima, media, and adventitia.

In the carotid of treated animals, a significant decrease is found in the cell count for smooth-muscle cells. The adventitia and the media showed a significant reduction in the cell count. As a result of a compound of formula I, a slight decrease in the absolute number of BrdU-labelled cells is seen in the intima, media, and adventitia during the first two labelling periods (0–72 and 72–96 h), and after 93–96 h a decrease in the number of labelled cells is seen in all compartments. Decreases in the number of smooth-muscle cells are likewise found in the aorta-denuded animals.

According to these findings, a compound of formula I can thus inhibit the proliferation, and especially the migration, of vascular smooth-muscle cells.

A compound of formula I is also capable of inhibiting angiogenesis. This may be demonstrated as follows: a chamber containing agar (0.8%) and heparin (2 U/ml) with or without growth factor (VEGF 3 μg/ml, PDGF 1 μg/ml or bFGF 0.3 μg/ml) is implanted subcutaneously into normal mice (C57 BL/6). A compound of formula I is administered orally in a dose showing good anti-tumour activity in a nude mouse xenotransplant model. Dosing is started one day before implantation of the chambers. The chambers are removed after 5 days. The angiogenic efficacy is quantified by measuring both the vascularised tissue which has grown around the implant and the blood content of this tissue (external blood). The blood is determined by measuring the haemoglobin. Although the vessels do not grow into the agar, the agar becomes intensely red if an antiangiogenic effect is present. If a compound inhibits the increase in blood that is induced by the growth factor, this is seen as an indication that the compound in question is blocking the angiogenic effect of the growth factor concerned. Inhibition of the weight but not the volume of blood suggests an effect on the proliferation of fibroblasts. A suppression of the control response suggests an inhibition of wound healing. At an oral dose of 50 mg/kg once daily, a compound of formula I inhibits the angiogenic effect of all three growth factors (VEGF, PDFG, bFGF).

Interestingly, it was found that 4-[(4-methyl-1-piperazinyl)-methyl]-*N*-{4-hydroxymethyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]-amino]-phenyl}-benzamide, 4-[(4-methyl-4-oxido-1-piperazinyl)-methyl]-*N*-{4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]-amino]-phenyl}-benzamide and 4-[(4-methyl-1-piperazinyl)-methyl]-*N*-[4-methyl-3-[[4-(1-oxido-3-pyridinyl)-2-pyrimidinyl]-amino]-phenyl]-benzamide represent metabolites of *N*-[4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-4-(4-methyl-piperazin-1-ylmethyl)-benzamide (STI571) which can be found

In the human body upon administration of STI571. STI571 is described in EP 0 564 409 B1 and, in the form of the methane sulfonate salt, in WO 99/03854.
In addition to the before-mentioned metabolites, further STI571 metabolites were identified in monkeys such as 4-[(4-methylcarbonyl-1-piperazinyl)-methyl]-*N*-{4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]-amino]-phenyl}-benzamide, 4-[(4-methyl-1-piperazinyl)-methyl]-*N*-{4-carboxy-3-[[4-(3-pyridinyl)-2-pyrimidinyl]-amino]-phenyl}-benzamide, 4-carboxy-*N*-{4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]-amino]-phenyl}-benzamide, 4-[(4-methyl-1-piperazinyl)-methyl]-*N*-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]-amino]-phenyl]-benzamide wherein the pyridinyl moiety is substituted at a ring carbon atom by hydroxy, and 4-[(1-piperazinyl)-methyl]-*N*-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]-amino]-phenyl]-benzamide wherein the pyridinyl moiety is substituted at a ring carbon atom by hydroxy.

Preference is given to compounds of formula I, wherein
R_1 is hydrogen,
R_2 is methyl or hydroxymethyl,
R_3 is methyl, and
the stars indicate the nitrogen atoms which optionally carry an oxygen atom to form the corresponding N-oxides,
with the proviso that at least one of the three nitrogen atoms marked by a star carries an oxygen atom if R_2 is methyl,
or salts of such compounds.

Special preference is further given to compounds of formula I, wherein
R_1 is hydrogen,
R_2 is hydroxy-lower alkyl,
R_3 is methyl, and
the stars indicate the nitrogen atoms which optionally carry an oxygen atom to form the corresponding N-oxides,
or salts of such compounds.

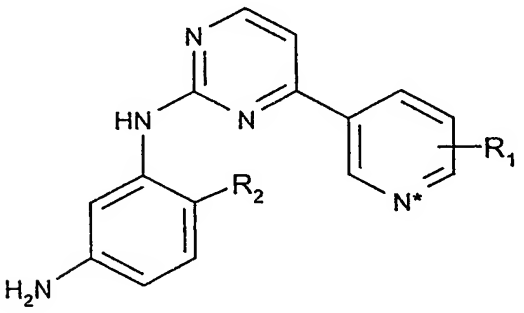
Especially preferred are the compounds selected from 4-[(4-methyl-1-piperazinyl)-methyl]-*N*-{4-hydroxymethyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]-amino]-phenyl}-benzamide, 4-[(4-methyl-4-oxido-1-piperazinyl)-methyl]-*N*-{4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]-amino]-phenyl}-benzamide and 4-[(4-methyl-1-piperazinyl)-methyl]-*N*-[4-methyl-3-[[4-(1-oxido-3-pyridinyl)-2-

pyrimidinyl]-amino]-phenyl]-benzamide, and pharmaceutically acceptable salts of these compounds.

Very special preference is further given to a compound of formula I mentioned in the Examples below, or a salt, especially a pharmaceutically acceptable salt, thereof.

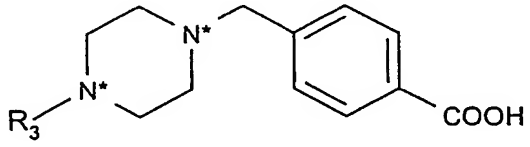
The compounds of formula I or salts thereof are prepared in accordance with processes known per se, though not previously described for the manufacture of the compounds of the formula I, especially whereby

a) a compound of formula II



(II),

wherein R_1 and R_2 have the meanings given under formula I and the star indicates a nitrogen atom which optionally carries an oxygen atom, is reacted with a compound of formula III

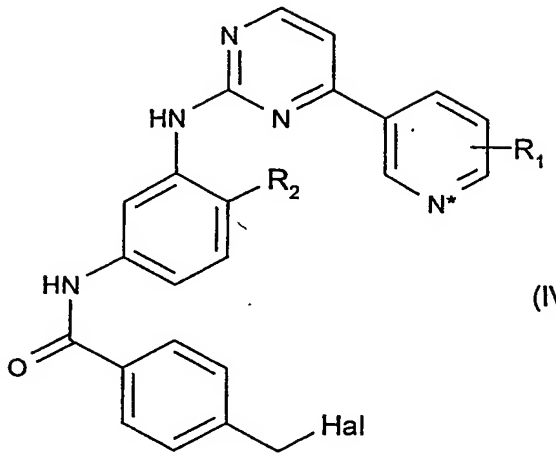


(III),

wherein R_3 has the meanings given under formula I and the stars indicate the nitrogen atoms which optionally carry an oxygen atom;

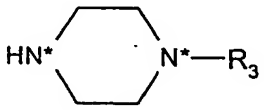
and a compound thus obtained is optionally converted into a N-oxide of formula I with a suitable oxidizing agent; or

b) a compound of formula IV



(IV),

wherein R_1 and R_2 have the meanings given under formula I, Hal is halo and the star indicates a nitrogen atom which optionally carries an oxygen atom, is reacted with a compound of formula V



(V),

wherein R_3 has the meanings given under formula I and the stars indicate the nitrogen atoms which optionally carry an oxygen atom;

and a compound thus obtained is optionally converted into a N-oxide of formula I with a suitable oxidizing agent;

whereby functional groups which are present in the starting compounds of process a) or b) and are not intended to take part in the reaction, are present in protected form if necessary, and protecting groups that are present are cleaved, whereby the said starting compounds may also exist in the form of salts provided that a salt-forming group is present and a reaction in salt form is possible;

and, if so desired, a compound of formula I obtained by process a) or b) is converted into another compound of formula I, an obtained free compound of formula I is converted into a salt, an obtained salt of a compound of formula I is converted into the free compound or another salt, and/or a mixture of isomeric compounds of formula I is separated into the individual isomers.

Description of the process variants

A suitable oxidizing agent for converting a compound obtained by process a) or b) into a N-oxide of formula I is preferably hydrogen peroxide or a suitable peracid, for example a suitable perbenzoic acid, such as especially m-chloro-perbenzoic acid. The reaction is carried out in an inert solvent, for example a halogenated hydrocarbon, such as dichloromethane, at temperatures of approximately from –20 °C to the boiling point of the solvent in question, in general below +100 °C. If hydrogen peroxide is used as the oxidizing agent, the reaction is preferably carried out in water at about room temperature. The desired N-oxide can then be purified using conventional methods such as e.g. column chromatography or recrystallisation.

On the other hand, the N-oxides of formula I may be prepared according to the process described in the preceding paragraph by already oxidizing the starting materials used in the synthesis of compounds of formula I.

Regarding process a):

The reaction between a compound of formula II and a compound of formula III preferably takes place in a suitable inert solvent, especially *N*,*N*-dimethylformamide, in the presence of propylphosphonic anhydride (Fluka, Buchs, Switzerland) and a base such as especially triethylamine, preferably at room temperature.

Regarding process b):

The reaction between a compound of formula IV and a compound of formula V preferably takes place in a suitable inert solvent, especially alcohols, e.g. lower alcohols such as especially ethanol, at elevated temperature, preferably near the boiling temperature of the solvent employed.

Halo present in a compound of formula IV is e.g. fluoro, chloro, bromo and iodo, preferably chloro.

Additional process steps

In the additional process steps, carried out as desired, functional groups of the starting compounds which should not take part in the reaction may be present in unprotected form or may be protected for example by one or more protecting groups. The protecting groups are then wholly or partly removed according to one of the known methods.

Protecting groups, and the manner in which they are introduced and removed are described, for example, in "Protective Groups in Organic Chemistry", Plenum Press, London, New York 1973, and in "Methoden der organischen Chemie", Houben-Weyl, 4th edition, Vol. 15/1, Georg-Thieme-Verlag, Stuttgart 1974 and in Theodora W. Greene, "Protective Groups in Organic Synthesis", John Wiley & Sons, New York 1981. A characteristic of protecting groups is that they can be removed readily, i.e. without the occurrence of undesired secondary reactions, for example by solvolysis, reduction, photolysis or alternatively under physiological conditions.

The end products of formula I may however also contain substituents that can also be used as protecting groups in starting materials for the preparation of other end products of formula I. Thus, within the scope of this text, only a readily removable group that is not a constituent of the particular desired end product of formula I is designated a "protecting group", unless the context indicates otherwise.

General process conditions

All process steps described here can be carried out under known reaction conditions, preferably under those specifically mentioned, in the absence of or usually in the presence of solvents or diluents, preferably those that are inert to the reagents used and able to dissolve them, in the absence or presence of catalysts, condensing agents or neutralising agents, for example ion exchangers, typically cation exchangers, for example in the protonated (H^+-) form, depending on the type of reaction and/or reactants at reduced, normal, or elevated temperature, for example in the range from -100 °C to about 190 °C, preferably from about -80 °C to about 150 °C, for example at -80 to -60 °C, at RT, at -20 to 40 °C, at 0 to 100 °C or at the boiling point of the solvent used, under atmospheric pressure or in a closed vessel, if need be under pressure, and/or in an inert, for example an argon or nitrogen, atmosphere.

The invention relates also to those embodiments of the process in which one starts from a

compound obtainable at any stage as an intermediate and carries out the missing steps, or breaks off the process at any stage, or forms a starting material under the reaction conditions, or uses said starting material in the form of a reactive derivative or salt, or produces a compound obtainable by means of the process according to the invention under those process conditions, and further processes the said compound *in situ*. In the preferred embodiment, one starts from those starting materials which lead to the compounds described hereinabove as preferred.

In the preferred embodiment, a compound of formula I is prepared according to the processes and process steps defined in the Examples.

The compounds of formula I, including their salts, are also obtainable in the form of hydrates, or their crystals can include for example the solvent used for crystallisation (present as solvates).

Starting materials

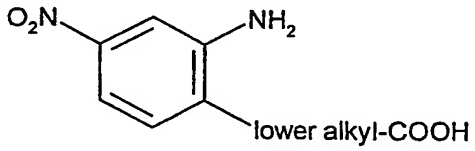
New starting materials and/or intermediates, as well as processes for the preparation thereof, are likewise the subject of this invention. In the preferred embodiment, such starting materials are used and reaction conditions so selected as to enable the preferred compounds to be obtained.

The starting materials used in the above described process are known, capable of being prepared according to known processes (see also EP 0 564 409 B1), or commercially obtainable; in particular, they can be prepared using processes as described in the Examples.

In the preparation of starting materials, existing functional groups which do not participate in the reaction should, if necessary, be protected. Preferred protecting groups, their introduction and their removal are described above or in the Examples. In place of the respective starting materials and transients, salts thereof may also be used for the reaction, provided that salt-forming groups are present and the reaction with a salt is also possible. Where the term starting materials is used hereinbefore and hereinafter, the salts thereof are always included, insofar as reasonable and possible.

A compound of formula II wherein R_2 is lower alkyl and the nitrogen atom marked by a star does not carry an oxygen atom as a substituent can be prepared as described in EP 0 564 409 B1. Such compounds may then be converted into the corresponding N-oxides using a suitable oxidizing agent as described above under "Description of the process variants".

A compound of formula II wherein R_2 is hydroxy-lower alkyl can be prepared analogously to Example 1 by starting with a compound of the following formula IV:



(VI).

The remaining starting materials are known, capable of being prepared according to known processes like those described in e.g. EP 0 564 409 B1, or commercially available; or in particular, they can be prepared using processes as described in the Examples.

The invention relates also to a process for the treatment of warm-blooded animals, including humans, suffering from said diseases, especially a tumour disease, wherein a quantity of a compound of formula I which is effective against the disease concerned, especially a quantity with antiproliferative and especially tumour-inhibiting efficacy, is administered to warm-blooded animals, including humans, in need of such treatment. The invention relates moreover to the use of a compound of formula I for the inhibition of the above-mentioned tyrosine kinases, especially PDGF receptor kinase, v-Abl kinase, and/or c-Kit receptor kinase, or for the preparation of pharmaceutical compositions for use in treating warm-blooded animals, including humans, especially for the treatment of tumours, such as gliomas, ovarian tumours, prostate tumours, colon tumours, and tumours of the lung, such as especially small cell lung carcinoma, and tumours of the breast or other gynaecological tumours. Depending on species, age, individual condition, mode of administration, and the clinical picture in question, effective doses, for example daily doses of about 1–2500 mg, preferably 1-1000 mg, especially 5-500 mg, are administered to warm-blooded animals, including humans, of about 70 kg bodyweight.

The invention relates also to pharmaceutical compositions comprising as an active ingredient a compound of formula I together with a pharmaceutically acceptable carrier, especially for the prevention or treatment of one of the said diseases, said pharmaceutical compositions being suitable for e.g. topical, enteral, for example oral or rectal, or parenteral administration. Especially tablets or gelatin capsules containing the active substance together with diluents, for example lactose, dextrose, sucrose, mannitol, sorbitol, cellulose, and/or glycerin, and/or lubricants, for example silica, talc, stearic acid, or salts thereof, typically magnesium or calcium stearate, and/or polyethylene glycol, are used for oral administration. Tablets may likewise contain binders, for example magnesium aluminium silicate, starches, typically corn, wheat or rice starch, gelatin, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone, and, if so desired, disintegrants, for example starches, agar, alginic acid, or a salt thereof, typically sodium alginate, and/or effervescent mixtures, or adsorbents, colouring agents, flavours, and sweetening agents. The pharmacologically active compounds of the present invention may further be used in the form of preparations for parenteral administration or infusion solutions. Such solutions are preferably isotonic aqueous solutions or suspensions, these possibly being prepared before use, for example in the case of lyophilised preparations containing the active substance either alone or together with a carrier, for example mannitol. The pharmaceutical substances may be sterilised and/or may contain excipients, for example preservatives, stabilisers, wetting agents and/or emulsifiers, solubilisers, salts for the regulation of osmotic pressure, and/or buffers. The present pharmaceutical compositions which, if so desired, may contain further pharmacologically active substances, such as other c-Kit inhibitors or inhibitors of VEGF receptor or c-Src activity, are prepared in a manner known per se, for example by means of conventional mixing, granulating, coating, dissolving or lyophilising processes, and contain from about 1% to 100%, especially from about 1% to about 20%, of the active substance or substances.

Examples:

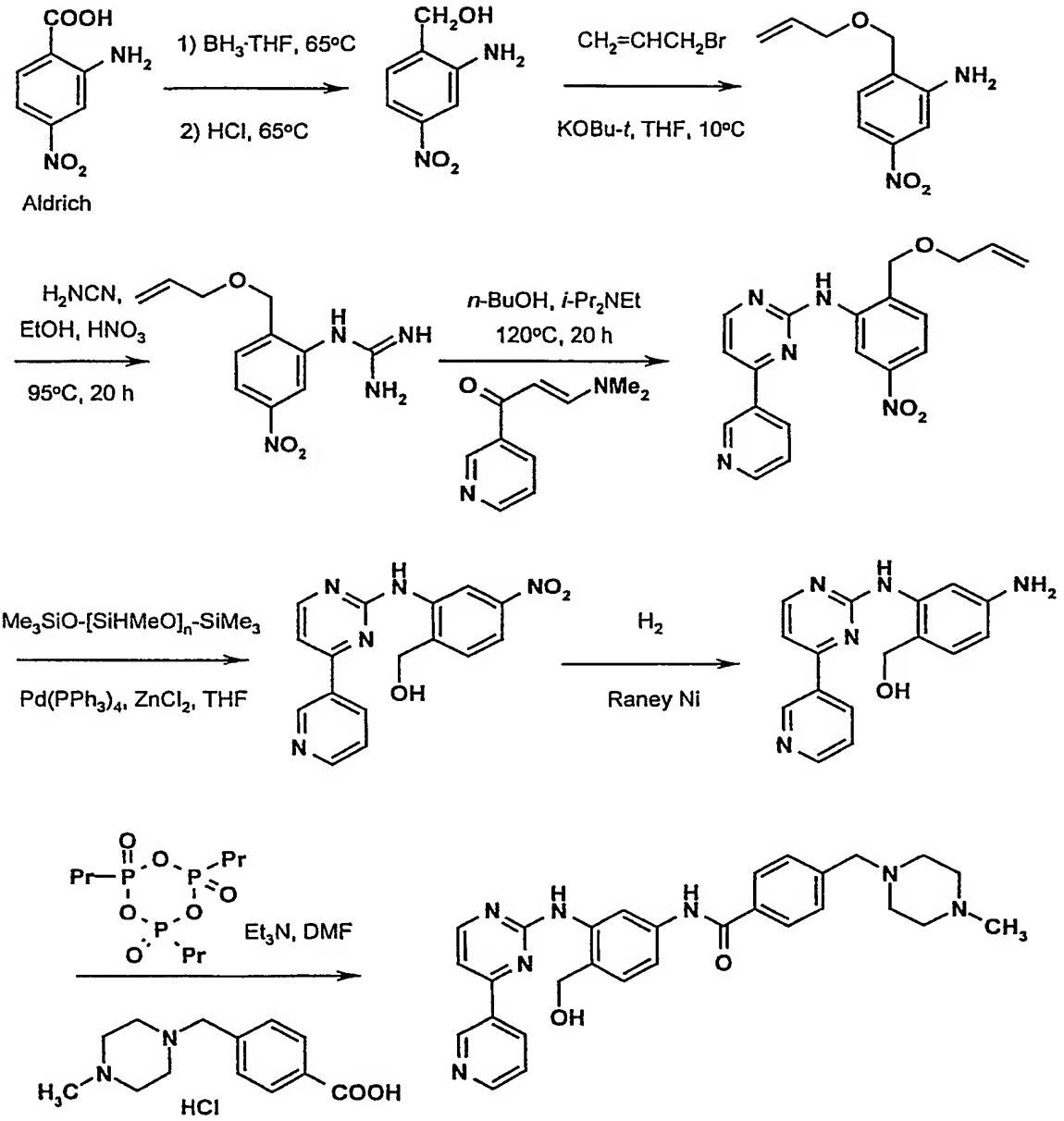
The following Examples illustrate the invention but do not limit the scope thereof in any way.

Abbreviations:

DMF	*N*,*N*-Dimethylformamide
h	hour(s)
min	minute(s)

m.p.	melting point
RT	room temperature
THF	tetrahydrofuran

Synthetic Scheme (Example 1):



Example 1: 4-[(4-Methyl-1-piperazinyl)-methyl]-*N*-{4-hydroxymethyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]-amino]-phenyl}-benzamide

A solution of propylphosphonic anhydride in *N*,*N*-dimethylformamide (Fluka, Buchs, Switzerland; 350 µL of 50%, 0.6 mmol) is added in portions over 20 min to a stirred mixture of *N*-(5-amino-2-hydroxymethyl-phenyl)-4-(3-pyridinyl)-2-pyrimidinamine (117 mg, 0.4 mmol),

4-[(4-methyl-1-piperazinyl)-methyl]-benzoic acid dihydrochloride (123 mg, 0.4 mmol) and triethylamine (445 µL, 3.2 mmol) in dry *N,N*-dimethylformamide (5 mL). The mixture is stirred for 24 h at RT. The solvent is evaporated off under reduced pressure and the residue is treated with saturated aqueous sodium hydrogen carbonate solution (20 mL) and extracted with ethyl acetate (2 x 20 mL). The combined extracts are washed with saturated aqueous sodium chloride (15 mL), dried ($MgSO_4$), filtered and the solvent is evaporated off under reduced pressure to yield the crude product which is purified by reverse phase high pressure liquid chromatography (Nagel Polygoprep C_{18}, 7 µm, 300 Å; Macherey-Nagel, Düren, Germany), eluent 0.1% trifluoroacetic acid in water - 0.1% trifluoroacetic acid in acetonitrile. The fractions containing the pure product are combined, basified with saturated aqueous sodium hydrogen carbonate and evaporated to dryness under reduced pressure. The residue is treated with saturated aqueous sodium hydrogen carbonate and extracted with ethyl acetate (5 x). The combined extracts are washed with water, dried ($MgSO_4$), filtered and the solvent is evaporated off under reduced pressure to yield the product which is recrystallised from methanol – ethyl acetate to give the title compound as a pale-yellow crystalline solid, m.p. 196-198°C.

^{1}H-NMR (500 MHz, DMSO-d_6, δ): 2.14 (s, 3H), 2.25-2.45 (m, 8H), 3.52 (s, 2H), 4.56 (s, 2H), 5.50 (br.s, 1H), 7.29 (d, J = 8.3 Hz, 1H), 7.41 (dd, J = 2.0, 8.3 Hz, 1H), 7.44 (d, J = 8.1 Hz, 2H), 7.50 (d, J = 5.1 Hz, 1H), 7.52 (dd, J = 3.3, 8.1 Hz, 1H), 7.93 (d, J = 8.1 Hz, 2H), 8.56 (d, J = 2.0 Hz, 1H), 8.57 (d, J = 5.1 Hz, 1H), 8.59 (ddd, J = 1.4, 2.1, 8.1 Hz, 1H), 8.69 (dd, J = 1.4, 3.3 Hz, 1H), 9.10 (s, 1H), 9.33 (d, J = 2.1 Hz, 1H) and 10.22 (s, 1H).

Step 1.1: 2-Amino-4-nitrobenzenemethanol

A stirred solution of 2-amino-4-nitrobenzoic acid (Aldrich; 18.2 g, 100 mmol) in dry THF (500 mL) at 20°C, is treated with a solution of borane-THF complex (BH_3·THF; Fluka; 100 mL of 1.0 M), dropwise over 45 min to regulate the gas evolution. The mixture is then heated at 65°C for 2 h. The stirred mixture is then cooled to 0°C, treated with water (20 mL) and warmed to RT. Upon the cessation of gas evolution, hydrochloric acid (20 mL of 12 M) is added and the mixture is then heated at 65°C for 30 min. The cooled mixture is then concentrated to a volume of *circa* 150 mL by rotary evaporation under reduced pressure to give a suspension. The suspension is filtered and the precipitate is redissolved in ethyl acetate (500 mL) and washed with saturated aqueous sodium hydrogen carbonate (2 x 150 mL). The solution is dried (Na_2SO_4), filtered and the solvent is evaporated off under reduced

pressure to yield the crude product which is purified by recrystallisation from ethyl acetate-hexane to give the title compound as a yellow crystalline solid, m.p. 126-128 °C.

Step 1.2: 2-[(2-Propenyloxy)-methyl]-5-nitrobenzenamine

A stirred solution of 2-amino-4-nitrobenzenemethanol (14.3 g, 85 mmol) in dry THF (350 mL) at 0°C under an argon atmosphere, is treated dropwise over 35 min with a solution of potassium *tert*-butylate in THF (Fluka; 85 mL of 1.0 M). The mixture is stirred at 0°C for 15 min and then treated dropwise over 50 min with a solution of allylbromide (7.9 mL, 94 mmol) in dry THF (80 mL) at 0°C and then stirred at 20°C for 90 min. The mixture is diluted with ethyl acetate (800 mL). The resulting solution is washed with saturated aqueous ammonium chloride (3 x 400 mL), dried ($MgSO_4$), filtered and the solvent is evaporated off under reduced pressure to yield the crude product which is purified by column chromatography on silica gel, eluent 50% ethyl acetate in hexane, to give the title compound as a brown oil. ^{1}H-NMR (500 MHz, DMSO-d_6, δ): 4.06 (d, J = 5.3 Hz, 2H); 4.47 (s, 2H); 5.22 and 5.34 (dd, J = 10.4, 17.3 Hz, 2H); 5.65 (br.s, 2H); 5.98 (m, J = 5.3, 10.4, 17.3 Hz, 1H), 7.35 (d, J = 8.3 Hz, 1H), 7.38 (dd, J = 2.0, 8.3 Hz, 1H) and 7.52 (d, J = 2.0 Hz, 1H).

Step 1.3: {2-[(2-Propenyloxy)-methyl]-5-nitrophenyl}-guanidine

Nitric acid (1.04 mL of 65%, 15 mmol) is added to a stirred solution of 2-[(2-propenyloxy)-methyl]-5-nitrobenzenamine (3.15 g, 15 mmol) in ethanol (30 mL) at 20°C. A solution of cyanamide (0.95 g, 22.5 mmol) in water (1 mL) is then added dropwise to the stirred mixture at 95°C over a period of 60 min. The mixture is heated at 95°C for 14 h, with additional aliquots of cyanamide (total 2.2 g, 58 mmol) being added throughout this period and with the acidity being periodically adjusted to pH 3 by the addition of nitric acid (65%). The resulting mixture is cooled to 0°C, basified with aqueous ammonia (5 mL of 25%), diluted with water (150 mL) and extracted with ethyl acetate (3 x 100 mL). The combined extracts are washed with saturated aqueous ammonium chloride (50 mL), dried ($MgSO_4$), filtered and the solvent is evaporated off under reduced pressure to give the title compound as a brown oil, which is used directly in the next step without further purification.

Step 1.4: *N*-{2-[(2-Propenyloxy)-methyl]-5-nitro-phenyl}-4-(3-pyridinyl)-2-pyrimidinamine

A stirred mixture of {2-[(2-propenyloxy)-methyl]-5-nitro-phenyl}-guanidine (3.75 g, 15 mmol), 3-(dimethylamino)-1-(3-pyridinyl)-2-propen-1-one (2.60 g, 15 mmol) and ethyl diisopropylamine (2.6 mL, 15 mmol) in 1-butanol (50 mL) is heated at 120°C for 20 h. The

solvent is then evaporated off under reduced pressure to give a residue which is dissolved in ethyl acetate (100 mL). The resulting mixture is filtered (celite), washed with saturated aqueous sodium chloride (50 mL), dried ($MgSO_4$), filtered and the solvent is evaporated off under reduced pressure to yield the crude product which is purified by column chromatography on silica gel, eluent ethyl acetate, and recrystallised from ethyl acetate-hexane to give the title compound as a yellow crystalline solid, m.p. 213-215°C.
^{1}H-NMR (500 MHz, DMSO-d_6, δ): 4.10 (d, J = 5.3 Hz, 2H); 4.77 (s, 2H); 5.22 and 5.35 (dd, J = 10.4, 17.3 Hz, 2H); 5.96 (m, J = 5.3, 10.4, 17.3 Hz, 1H), 7.58 (dd, J = 4.8, 7.9 Hz, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.69 (d, J = 5.2 Hz, 1H), 7.95 (ddd, J = 1.2, 1.2, 7.9 Hz, 1H), 8.51 (dd, J = 1.6, 8.4 Hz, 1H), 8.67 (d, J = 5.2 Hz, 1H), 8.73 (dd, J = 1.2, 4.8 Hz, 1H), 9.05 (d, J = 1.2 Hz, 1H), 9.23 (br.s, 1H) and 9.35 (d, J = 1.6 Hz, 1H).

Step 1.5: *N*-(2-Hydroxymethyl-5-nitro-phenyl)-4-(3-pyridinyl)-2-pyrimidinamine
Polymethylhydrosiloxane (860 mg), tetrakis(triphenylphoshine)palladium (70 mg) and zinc chloride (2.66 mL of 0.5 M in THF, 1.33 mmol) is added to a stirred solution of *N*-{2-[(2-propenyloxy)-methyl]-5-nitro-phenyl}-4-(3-pyridinyl)-2-pyrimidinamine (2.60 g, 7.2 mmol) in dry THF (60 mL). The mixture is then stirred under an argon atmosphere at 30°C for 30 h. The solvent is then evaporated off under reduced pressure to give a residue which is treated with saturated aqueous sodium chloride solution (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined extracts are dried (Na_2SO_4), filtered and the solvent is evaporated off under reduced pressure to yield the crude product which is recrystallised from THF to give the title compound as a pale-yellow crystalline solid, m.p. 247-250°C.

Step 1.6: *N*-(5-Amino-2-hydroxymethyl-phenyl)-4-(3-pyridinyl)-2-pyrimidinamine
A solution of *N*-(2-hydroxymethyl-5-nitro-phenyl)-4-(3-pyridinyl)-2-pyrimidinamine (0.23 g, 0.71 mmol) in ethanol (230 mL) is hydrogenated at atmospheric pressure over Raney nickel (0.2 g) at 25°C. The calculated amount of hydrogen is taken up in 13 h. The mixture is then filtered and the solvent is evaporated off under reduced pressure to yield the crude product which is purified by column chromatography on silica gel, eluent 25% aqueous ammonia-ethanol-dichloromethane (1:9:90), to give the title compound as a yellow crystalline solid, m.p. 213-215°C.
^{1}H-NMR (500 MHz, DMSO-d_6, δ): 4.42 (d, J = 5.1 Hz, 2H), 5.05 (br.s, 2H), 5.26 (t, J = 5.1 Hz, 1H), 6.23 (dd, J = 2.1, 8.0 Hz, 1H), 6.91 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 2.0 Hz, 1H), 7.45 (d, J = 5.1 Hz, 1H), 7.56 (dd, J = 4.7, 8.0 Hz, 1H), 8.47 (ddd, J = 1.8, 1.8, 8.0 Hz, 1H),

8.53 (d, J = 5.1 Hz, 1H), 8.70 (dd, J = 1.4, 4.7 Hz, 1H), 8.88 (s, 1H) and 9.29 (d, J = 2.4 Hz, 1H).

Example 2: 4-[(4-Methyl-4-oxido-1-piperazinyl)-methyl]-*N*-{4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]-amino]-phenyl}-benzamide

3-Chloroperoxybenzoic acid (Fluka, Buchs, Switzerland; 2.06 g of 55%, 4.27 mmol) is added to a stirred mixture of 4-[(4-methyl-1-piperazinyl)-methyl]-*N*-{4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]-amino]-phenyl}-benzamide (prepared as described in EP 0 564 409 B1, Example 21; 2.00 g, 4.05 mmol) in dichloromethane (70 mL) at -20°C. The resulting mixture is then stirred at RT for 72 h. The solvent is then evaporated off under reduced pressure to yield a mixture which is purified by column chromatography on silica gel, eluent dichloromethane-methanol-water (70:30:5), to give the title compound as a yellow crystalline solid, m.p. 154 - 158°C.

Example 3: 4-[(4-Methyl-1-piperazinyl)-methyl]-*N*-[4-methyl-3-[[4-(1-oxido-3-pyridinyl)-2-pyrimidinyl]-amino]-phenyl]-benzamide

N-Methylpiperazine (99 mg, 1.0 mmol) is added to a stirred suspension of 4-chloromethyl-*N*-[4-methyl-3-[[4-(1-oxido-3-pyridinyl)-2-pyrimidinyl]-amino]-phenyl]-benzamide (220 mg, 0.49 mmol) in ethanol (5 mL). The mixture is then stirred at 100°C for 15 h to give a solution, which is then cooled to RT and treated with ethyl acetate (200 mL). The resulting solution is washed with aqueous sodium hydroxide (100 mL of 2M) and saturated aqueous sodium chloride solution (100 mL), dried (Na_2SO_4), filtered and the solvent is evaporated off under reduced pressure to yield the crude product which is purified by column chromatography on silica gel, eluent 25% aqueous ammonia-methanol-dichloromethane (0.5:10:90) to give the title compound as a yellow crystalline solid, m.p. 232-235°C.

Step 3.1: *N*-[4-Methyl-3-[[4-(1-oxido-3-pyridinyl)-2-pyrimidinyl]-amino]-phenyl]-benzamide

Utilising the procedure described in Example 2, but employing *N*-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]-amino]-phenyl]-benzamide (prepared as described in EP 0 564 409 B1, Example 20) in place of 4-[(4-methyl-1-piperazinyl)-methyl]-*N*-{4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]-amino]-phenyl}-benzamide, afforded the title compound which is purified by column chromatography on silica gel, eluent 10% methanol in dichloromethane, and recrystallised from ethanol to give the title compound as a pale-yellow crystalline solid, m.p. 258 – 260°C.

Step 3.2: 4-Methyl-*N*-3-[4-(1-oxido-3-pyridinyl)-2-pyrimidinyl]-1,3-benzenediamine

Hydrochloric acid (9 mL of 4M) is added to a suspension of *N*-[4-methyl-3-[[4-(1-oxido-3-pyridinyl)-2-pyrimidinyl]-amino]-phenyl]-benzamide (0.43 g, 1.08 mmol) in *n*-propanol (9 mL) and the resulting mixture is heated at 100°C for 34 h. The cooled mixture is evaporated under reduced pressure to give an oil, which is dissolved in water (10 mL), filtered and basified with aqueous sodium hydroxide (4 M). The resulting precipitate is filtered, washed with water and dried to yield the crude product, which is recrystallised from ethanol to give the title compound as a yellow crystalline solid, m.p. 104-106°C.

Step 3.3: 4-Chloromethyl-*N*-[4-methyl-3-[[4-(1-oxido-3-pyridinyl)-2-pyrimidinyl]-amino]-phenyl]-benzamide

A solution 4-(chloromethyl)-benzoyl chloride (Fluka, Buchs, Switzerland; 184 mg, 0.977 mmol) in dioxane (2 mL) is added dropwise to a solution of 4-methyl-*N*-3-[4-(1-oxido-3-pyridinyl)-2-pyrimidinyl]-1,3-benzenediamine (275 mg, 0.937 mmol) in dioxane (5 mL) and the mixture is stirred at 20°C for 75 min. A second portion of 4-(chloromethyl)-benzoyl chloride (60 mg, 0.317 mmol) dissolved in dioxane (1 mL) is then added and the mixture is stirred for a further 120 min. The resulting suspension is treated with ethyl acetate (50 mL) to give a solution which is washed with aqueous sodium hydroxide (2 x 50 mL of 2M). The ethyl acetate solution is dried (Na_2SO_4), filtered and the solvent is evaporated off under reduced pressure to yield the crude product which is purified by column chromatography on silica gel, eluent 5% methanol in dichloromethane to give the title compound as a yellow crystalline solid, m.p. 224-226°C.

Example 4: 4-[(4-Methyl-1,4-dioxido-1-piperazinyl)-methyl]-*N*-{4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]-amino]-phenyl}-benzamide

4-[(4-Methyl-1-piperazinyl)-methyl]-*N*-{4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]-amino]-phenyl}-benzamide monomethanesulphonate (3.00 g, 5 mmol; prepared as described in WO 99/03854) is added to aqueous hydrogen peroxide (30 mL of 3%) and the resulting solution is stirred at 20°C for 160 h. The pH of the solution is then adjusted to pH 14 with aqueous sodium hydroxide (4 M) and the resulting suspension is stirred for 1.5 h. The crude product is filtered off, washed with water, dried and purified by column chromatography on silica gel, eluent 25% aqueous ammonia-ethanol-dichloromethane (5:30:70), to give the title compound as a yellow crystalline solid, m.p. 242-244°C.

Example 5:

Tablets containing 100 mg of a compound of formula I, for example one of the compounds of formula I described in the Examples 1-4, are usually prepared in the following composition:

Composition:

Active ingredient	100 mg
Crystalline lactose	240 mg
Avicel	80 mg
PVPPXL	20 mg
Aerosil	2 mg
Magnesium stearate	5 mg
	447 mg

Preparation: The active substance is mixed with carrier materials and compressed on a tableting machine (Korsch EKO, punch diameter 10 mm).
Avicel is microcrystalline cellulose (FMC, Philadelphia, USA).
PVPPXL is polyvinylpolypyrrolidone, cross-linked (BASF, Germany).
Aerosil is silicon dioxide (Degussa, Germany).

Example 6:

Capsules containing 100 mg of a compound of formula I, for example one of the compounds of formula I described in the Examples 1-4, are usually prepared in the following composition:

Composition:

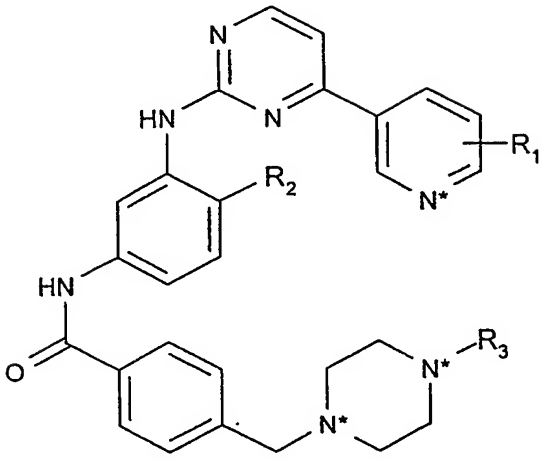
Active ingredient	100 mg
Avicel	200 mg
PVPPXL	15 mg
Aerosil	2 mg
Magnesium stearate	1.5 mg

318.5 mg

Preparation: The capsules are prepared by mixing the components and filling the mixture into hard gelatin capsules, size 1.

What is claimed is:

1. A compound of formula I



(I),

wherein

R_1 is hydrogen or hydroxy,

R_2 is lower alkyl or hydroxy-lower alkyl,

R_3 is hydrogen, methyl or acetyl, and

the stars indicate the nitrogen atoms which optionally carry an oxygen atom to form the corresponding N-oxides,

with the proviso that at least one of the three nitrogen atoms marked by a star carries an oxygen atom if R_1 is hydrogen, R_2 is methyl and R_3 is hydrogen or methyl,

or a salt thereof.

2. A compound of formula I according to claim 1, wherein

R_1 is hydrogen,

R_2 is methyl or hydroxymethyl,

R_3 is methyl, and

the stars indicate the nitrogen atoms which optionally carry an oxygen atom to form the corresponding N-oxides,

with the proviso that at least one of the three nitrogen atoms marked by a star carries an oxygen atom if R_2 is methyl,

or a salt thereof.

3. A compound of formula I according to claim 1, wherein
R_1 is hydrogen,
R_2 is hydroxy-lower alkyl,
R_3 is methyl, and
the stars indicate the nitrogen atoms which optionally carry an oxygen atom to form the corresponding N-oxides,
or a salt thereof.

4. A compound of formula I according to claim 2 which is 4-[(4-methyl-4-oxido-1-piperazinyl)-methyl]-*N*-{4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]-amino]-phenyl}-benzamide, or a pharmaceutically acceptable salt thereof.

5. A compound of formula I according to claim 2 which is 4-[(4-methyl-1-piperazinyl)-methyl]-*N*-[4-methyl-3-[[4-(1-oxido-3-pyridinyl)-2-pyrimidinyl]-amino]-phenyl]-benzamide, or a pharmaceutically acceptable salt thereof.

6. A compound of formula I according to claim 2 which is 4-[(4-methyl-1,4-dioxido-1-piperazinyl)-methyl]-*N*-{4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]-amino]-phenyl}-benzamide, or a pharmaceutically acceptable salt thereof.

7. A compound of formula I according to claim 2 or 3 which is 4-[(4-methyl-1-piperazinyl)-methyl]-*N*-{4-hydroxymethyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]-amino]-phenyl}-benzamide, or a pharmaceutically acceptable salt thereof.

8. A compound according to any one of claims 1 to 7 or a pharmaceutically acceptable salt thereof for use in a method for the therapeutic treatment of warm-blooded animals, including humans.

9. A pharmaceutical composition comprising a compound according to any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier.

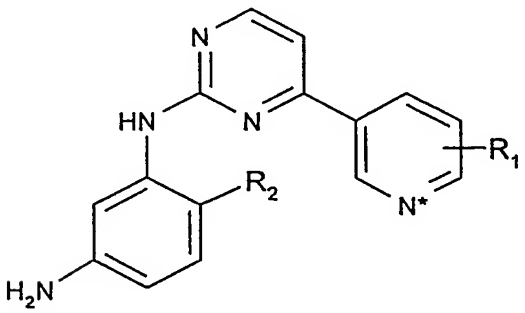
10. A pharmaceutical composition for the treatment of a proliferative disorder in warm-blooded animals, including humans, comprising as an active ingredient a compound of formula I according to any one of claims 1 to 7 or a pharmaceutically acceptable salt of such a compound, together with a pharmaceutically acceptable carrier.

11. Use of a compound of formula I according to any one of claims 1 to 7 or a pharmaceutically acceptable salt of such a compound for the preparation of a pharmaceutical composition for the treatment of a proliferative disorder.

12. Use of a compound of formula I according to any one of claims 1 to 7 or a pharmaceutically acceptable salt of such a compound for the treatment of a proliferative disorder.

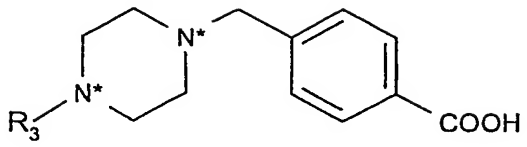
13. A method of treating warm-blooded animals, including humans, which comprises administering to such a warm-blooded animal suffering from a proliferative disorder, in a dose effective against said disorder, a compound of formula I according to any one of claims 1 to 7 or a pharmaceutically acceptable salt of such a compound.

14. A process for the preparation of a compound of formula I according to claim 1 or a salt thereof, characterized in that a compound of formula II



(II),

wherein R_1 and R_2 have the meanings as defined for a compound of formula I according to claim 1 and the star indicates a nitrogen atom which optionally carries an oxygen atom, is reacted with a compound of formula III



(III),

wherein R_3 has the meanings as defined for a compound of formula I according to claim 1 and the stars indicate the nitrogen atoms which optionally carry an oxygen atom;

and a compound thus obtained is optionally converted into a N-oxide of formula I with a suitable oxidizing agent;

whereby functional groups which are present in the compounds of formula II and III and are not intended to take part in the reaction, are present in protected form if necessary, and protecting groups that are present are cleaved, whereby the compounds of formula II and III may also exist in the form of salts provided that a salt-forming group is present and a reaction in salt form is possible;

and, if so desired, a compound of formula I thus obtained is converted into another compound of formula I, an obtained free compound of formula I is converted into a salt, an obtained salt of a compound of formula I is converted into the free compound or another salt, and/or a mixture of isomeric compounds of formula I is separated into the individual isomers.